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Clinical uses of intravenous immunoglobulin

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Introduction

Intravenous immunoglobulin (IVIG) is a blood product prepared from the serum of between 1000 and 15 000 donors per batch. It is the treatment of choice for patients with antibody deficiencies. For this indication, IVIG is used at a 'replacement dose' of 200–400 mg/kg body weight, given approximately 3-weekly. In contrast, 'high dose' IVIG (hdIVIG), given most frequently at 2 g/kg/month, is used as an 'immunomodulatory' agent in an increasing number of immune and inflammatory disorders. Initial use of hdIVIG was for immune thrombocytopenic purpura (ITP) in children [1].

The clinical specialities using the largest amounts of IVIG are neurology, haematology, immunology, nephrology, rheumatology and dermatology. IVIG has had a major impact on the treatment of neurological disorders including dermatomyositis, Guillain–Barre syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), myasthenia gravis and stiff person syndrome. In haematology it is used to treat immune cytopenias, parvovirus B19 associated red cell aplasia, hypogammaglobulinaemia secondary to myeloma and chronic lymphatic leukaemia and post-bone marrow transplantation. In immunology IVIG is used in the treatment of primary antibody deficiency (PAD), in nephrology, rheumatology and ophthalmology it has been used to treat vasculitis, systemic lupus erythematosis (SLE), mucous membrane pemphigoid and uveitis and in dermatology it is used most commonly to treat Kawasaki syndrome, dermatomyositis, toxic epidermal necrolysis and the blistering diseases (Table 1).

In this paper, we review recent developments in the understanding of mechanisms of action of IVIG, the major current clinical areas of use concentrating on conditions with a better established evidence base and discuss emerging areas of use of IVIG.

Mechanism of action of IVIG

The mechanisms of action of therapeutic immunoglobulin are complex, but over recent years important advances in understanding have been made (summarized in Fig. 1) [2]; the predominant mechanism operating in a particular situation appears to depend on both the immunoglobulin dose and the pathogenesis of the disease under consideration.

Effects due to $F(ab')_2$

Commercial IVIG preparations contain a 'species repertoire' of antibody specificities, resulting in neutralization of a wide range of antigens including pathogens and superantigens [3]; there is, however, significant batch-to-batch variation in the concentration of a particular antibody [4]. IVIG has been shown to have a considerable inhibitory effect on mitogen-induced T cell proliferation *in vitro* [5]. This effect has been shown for intact IgG, with less evidence for a role for Fc fragment [6]. Both antigen-dependent and antigen-independent responses are inhibited by IVIG in a dose-dependent manner [7].

IVIG has been shown to suppress the proliferation of antigen-specific T cells without inducing apoptosis, the cells remaining refractory to induction of apoptosis by CD95 ligation [8]. In toxic epidermal necrolysis (TEN), which is mediated by over-expression of fas-ligand, inducing apoptosis in keratinocytes, causing extensive dermal/epidermal separation, IVIG contains fas-blocking antibodies reducing keratinocyte death in this condition [9]. In addition in atopic dermatitis T cell-mediated, Fas-induced keratinocyte

Table 1. Major uses of intravenous imunoglobulin (IVIG).

Neurology	Haematology	Immunology	Dermatology	Nephrology rheumatology, opthalmology and other
Guillain Barre syndrome (RCT and CR)	Immune thrombocytopenia (RCT)	Primary antibody deficiencies (XLA, CVID, HIGM, WAS and others)	Kawasaki syndrome (RCT)	Vasculitis (RCT)
Multifocal motor neuropathy (RCT)	Post bone marrow transplant (RCT)	Secondary antibody deficiencies (myeloma, CLL (RCT), drugs and other causes)	Dermatomyositis (RCT)	Sysytemic lupus erythematosis
Chronic inflammatory demyelinating polyneuropathy (RCT)	Myeloma and chronic lymphocytic leukaemia (RCT)		Toxic epidermal necrolysis	Streptococcal toxic shock syndrome
Dermatomyositis and inflammatory myopathies (RCT)	Parvovirus B19-associated aplasia		Blistering diseases*	Birdshot retinochoroidopathy
Myasthenia gravis (RCT)	Immune neutropenia		Immune urticaria	Autoimmune uveitis
Lambert–Eaton syndrome (RCT)	Immune haemolytic anaemia		Atopic dermatitis	Mucous membrane pemphigoid
Stiff person syndrome (RCT)			Scleromyxoedema Pyoderma gangrenosum	

IVIG is used mainly at high dose (2 g/kg) for the indications listed in neurology, haematology, rheumatology, dermatology and others while in immunology replacement doses (0·4 g/kg) are given. The uses listed are not exhaustive, but aim to cover the disorders for which IVIG is most frequently used and whether a randomized controlled (RCT) study or Cochrane review (CR) is available. CVID, common variable immunodeficiency; XLA, X-linked agammaglobulinaemia; HIGM, hyper-IgM syndrome; WAS, Wiskott Aldrich syndrome; CLL, chronic lymphocytic leukaemia. *Blistering diseases include pemphigus vulgaris, pemphigus folaceous, bullous and nodular pemphigoid, mucous membrane pemphigoid, gestational pemphigoid, epidermolysis bullosa acquisita and linear IgA disease.

apoptosis is inhibitied by IVIG [10]. Additional studies show that IVIG causes the arrest of cells at the G0/G1 phase of the cell cycle, and inhibits cells from entering S-phase [11]. In contrast to these studies IVIG has been demonstrated to induce apoptosis in leukaemic lymphocytes and monocytes as well as normal tonsillar B cells, an effect mediated at least in part by anti-CD95 antibodies present within the IVIG preparations [12]. Taken together, these studies show that although IVIG appears to be broadly anti-apoptotic and cause cell cycle arrest, under certain conditions it may also induce apoptosis.

IVIG has also been shown to reduce adhesion of T cells to extracellular matrix following activation by phytohaemagglutinin (PHA) or phorbol myristate acetate (PMA) [13] and contains antibodies to the Arg-Gly-Asp (RGD) motif, the attachment site for a number of adhesive extracellular matrix proteins and β1, β3 and β5 integrins [14].

IVIG contains natural IgG antibodies which are germline encoded and occur in the absence of infection or vaccination and the importance of these has been demonstrated in a study into the *in vitro* differentiation of dendritic cells (DCs) from patients with X-linked agammaglobulinaemia who lack B cells and antibodies. Differentiation of DCs was shown to be impaired, and the defect was reversed by natural antibodies reactive with CD40 [15]. Anti-idiotypes present in IVIG may also be responsible for the success of IVIG treatment of ITP; IVIG prepared from multiparous women contains many more anti-idiotypes to human HLA antigens, and can inhibit alloimmunization to HLA [16]. IVIG may also contain antibodies to a range of immunologically important molecules such as interleukin (IL)-1α, tumour necrosis factor (TNF)-α and interferon (IFN)-γ [17–19] as these have been demonstrated in the sera of healthy individuals. IVIG contains antibodies against the beta chain of the T cell receptor and also against CD5 and CD4 [20–22]

Effects due to Fc receptor binding

The binding of immunoglobulin Fc to inhibitory (FcγRIIb) and activating (FcγRI and FcγRIII) Fc receptors exerts numerous effects. Competitive binding of IVIG to FcR on macrophages in the reticuloendothelial system may alter clearance of cells in autoimmune cytopenias [23]. FcγRIII are particularly involved and the Fc region of the Ig is essential [24]. Binding of IVIG to FcγRIIb deactivates phagocytosis. Bruhns and colleagues demonstrated recently that this process involves colony stimulating factor (CSF)-1 dependent macrophages which they claimed act as 'sensors' for IVIG Fc regions [25]. This results in the induction of FcγRIIb on CSF-1 independent macrophages, which in turn raises

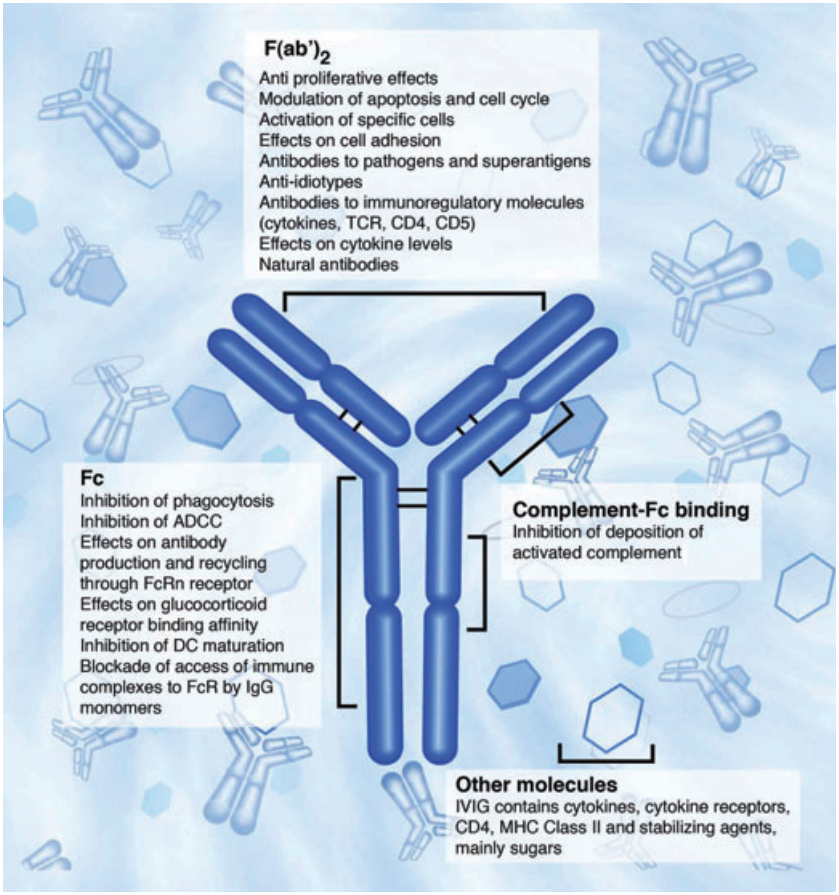

Fig. 1. Immunomodulatory actions of intravenous immunoglobulin. Intravenous immunoglobulin (IVIG), may for the purposes of understanding, be thought of as four separate components: (1) actions mediated by the variable regions $F(ab')_2$, (2) actions of Fc region on a range of Fc receptors (FcR), (3) actions mediated by complement binding within the Fc fragment and (4) immunomodulatory substances other than antibody in the IVIG preparations. It should be remembered that not all the potential mechanisms of action fit perfectly into the groupings and that several mechanisms may act concurrently (TCR, T cell receptor; ADCC, antibody dependent cellular cytotoxicity; DC, dendritic cell).

the threshold for FcγRIII-mediated activation and inflammation. FcR binding has been shown to inhibit dendritic cell maturation at immunomodulatory doses [26]. FcR may be important in cytokine changes which down-regulate reticuloendothelial function [27]. The interpretation of changes in cytokine levels following IVIG is complicated by the different methodologies used in measurement, the presence of antagonists or soluble receptors and *in vitro versus in vivo* data. IVIG has been shown to induce IFN-γ, IL-6 and IL-1ra (IL-1ra by up to 1000 fold), while IL-1 and IL-2 are down-regulated [28–32]. Changes in cytokines may also be affected by the pattern of expression prior to IVIG and the effect *in vivo* is difficult to predict from *in vitro* studies.

IVIG may interfere with antibody dependent cellular cytotoxicity (ADCC) by competing for Fc receptor binding with antibodies directed towards cellular targets. In addition, monomeric IgG within IVIG may block access of aggregated IgG to FcγRIII. IVIG can also act synergistically with dexamethasone in suppressing lymphocyte activation as measured by a shift in the dexamethasone dose–response curve by 1 log-fold; this was associated with significantly improved glucocorticoid receptor binding affinity [33].

Saturation of the neonatal FcR (FcRn) may enhance endogenous IgG catabolism, reducing autoantibody levels by as much as 40% in some models [34]. Low-affinity FcR (FcγRII and III) saturation by monomeric IgG occurs at clinically achievable levels, even though these are predominantly receptors for aggregated IgG. This suggests that functional blockade of low affinity FcR is important [35].

The relative abundance of activating and inhibiting FcR, and hence the response to IVIG, is influenced by the cytokine balance. Th1 cytokines including IFN-γ and TNF-α induce activating FcR, and down-regulate inhibitory FcR. Th2 cytokines including IL-4 and IL-13 have the opposite effect. Clinically this is reflected in the response of patients with childhood immune thrombocytopenia (ITP) to IVIG, in that patients who go into remission tend to have induction of Th2 cytokines. This differential control of FcR expression, and hence response to IVIG, may be due to cross-linking of FcRI on macrophages which down-regulates IL-12 production and hence Th1 cytokines.

Effects on complement-Fc binding

Other IVIG effects include modulation of complement activity, demonstrated particularly by the effects of IVIG in dermatomyositis, a complement-dependent microangiopathy. Although in fact beneficial, IVIG as well as immune complexes results in the generation of nascent C3b, and should theoretically be proinflammatory. Indeed small

doses of IVIG produce measurable classical and alternative pathway activation [36]. However, the Fc region appears to scavenge C3a and C5a [37]. High-dose IVIG inactivates immune complexes, selectively attenuating complement amplification.

Other substances present in IVIG preparations

IVIG itself may contain cytokines and other molecules including soluble cytokine inhibitors, soluble CD4 and major histocompatibility complex (MHC) class II [38]. Stabilizing agents, mainly various sugars, can also exert an effect, both maltose and sucrose, at concentrations present in commercial IVIG preparations, can inhibit PHA- and to a lesser extent, PMA-induced proliferative responses *in vitro* [39] (reviewed in [2]).

Haematological

Immunoglobulin therapy first established itself as an immunomodulatory agent in the management of (ITP) [23], although in adult ITP several studies now suggest that steroids alone can increase the platelet count unless clinical features of haemorrhage have developed [40]. Haemolytic anaemia in sickle cell disease and after transfusion in lymphoma can occur despite being direct antiglobulin test (DAT) and alloantibody negative. Provan outlines how IVIG was shown to prevent this form of anaemia in a small series of three patients from Win's group described in poster form only – suggesting that other mechanisms, apart from FcR blockade, are also relevant [41].

Acquired haemophilia has also been shown to respond to hdIVIG therapy [42]. However, despite initial success a recent meta-analysis suggests that hdIVIG is still associated with a poor complete response rate and is not recommended as first line therapy.

Haematologists have traditionally used IVIG to prevent cytomegalovirus (CMV) infection following bone marrow transplantation (BMT). Mühleisen and colleagues showed that infection rates and survival are similar, whether or not IVIG is given [41]. IVIG should probably be reserved only for patients who are hypogammaglobulinaemic (IgG < 4 g/l) after BMT. Paediatricians have used IVIG at 0·5 g/kg in a single dose on the first day of life in children with haemolytic disease of the newborn [43]. This is effective at reducing haemolysis and hence reduces the need for exchange transfusions. Adults with secondary antibody deficiency (SAD) associated with chronic lymphocytic leukaemia and myeloma have both been shown to benefit from IVIG replacement therapy, if incapable of mounting an adequate response to diagnostic immunization with polysaccharide antigens (Pneumovax II) [44,45]. Although the clinical efficacy of IVIG replacement in SAD is accepted, its cost-effectiveness has been questioned [46]. Continuous antibiotic prophylaxis with cotrimoxazole alone has been shown to be effective in early myeloma, albeit with a significant incidence of adverse effects [47], thus prompting calls for randomised trials comparing antibiotic prophylaxis alone with IVIG in these disease groups. The impact of immunization with the new pneumococcal conjugate vaccine (Prevenar) on the incidence of pneumococcal disease in patients with CLL and myeloma is yet to be assessed.

IVIG in autoimmune neurological disease

Guillain–Barre syndrome

A considerable body of evidence summarized in a Cochrane systematic review [48] has shown that IVIG is equally efficacious to plasma exchange in the treatment of patients with acute paralytic Guillain–Barre syndrome (GBS). Whether IVIG is effective in adults with mild disease or in those who start treatment more than 2 weeks after the onset of symptoms is uncertain. There is no evidence that combining IVIG with preceding plasma exchange is of added benefit. Equally, combining pulse steroids with IVIG offers no extra benefit [49]. Although there are no randomized trials of IVIG in childhood GBS the evidence from adult trials has been sufficiently persuasive for IVIG to be recommended for children with GBS.

Multifocal motor neuropathy with conduction block

Multifocal motor neuropathy (MMN) presents with asymmetrical distal muscle weakness which maybe mistaken for motor neurone disease but is distinguished electrophysiologically by the presence of localized motor conduction block. IVIG is the treatment of choice in MMN as steroids have little effect and may worsen disease. Several randomized controlled trials [50,51] have shown that IVIG improves muscle strength, neurological disability scores and may reverse conduction block. Long-term maintenance IVIG therapy is beneficial in many patients [51].

Chronic inflammatory demyelinating neuropathy (CIDP)

This is a progressive symmetrical neuropathy characterized clinically by proximal and distal weakness, sensory loss and areflexia. IVIG is increasingly supplanting steroids (combined in some cases with plasma exchange), hitherto the traditional treatment for CIDP. Evidence from randomized controlled trials [52,53] indicates that IVIG is of equal efficacy to steroids and plasma exchange, at least in the short term. Increasingly, IVIG is preferred as first-line therapy for CIDP given the morbidity associated with long-term steroid therapy. Indeed, patients with MMN and those with pure motor CIDP may deteriorate after steroids. Whether combined treatment with IVIG and steroids offers added benefit is unknown.

Dermatomyositis and other inflammatory myopathies

The proximal inflammatory myopathy that is characteristic of dermatomyositis (DM) is immunopathogenetically associated with a complement-dependent microangiopathy in affected muscles. The benefits of IVIG in patients with DM refractory to standard immunosuppressive therapy was shown in a randomized placebo-controlled trial in 1993 [54]. Whether IVIG is superior to steroids as first-line therapy for DM is unknown.

In refractory polymyositis, IVIG has been shown to be useful in open trials but has not been subjected to a randomized trial. Evidence from randomized trials does not support the use of IVIG in inclusion body myositis.

Defects of the neuromuscular junction

Myasthenia gravis (MG), an archetypal autoimmune neurological disorder is characterized by fluctuating, fatiguable muscle weakness caused by antibodies to the acetylcholine receptor. The only RCT [55] to date showed that IVIG was as effective as plasma exchange for myasthenic exacerbations. In practice, IVIG is reserved for patients with MG refractory to or intolerant of standard therapy or in place of plasma exchange.

Lambert–Eaton syndrome (LEMS)

The Lambert–Eaton syndrome which presents with a mixture of myopathic and myasthenic features is associated strongly with antibodies to voltage-gated calcium channels (VGCC). LEMS is associated with underlying small-cell lung carcinoma in about 60% of patients in whom it acts as a para-neoplastic marker. IVIG has been shown in a RCT to produce short-term improvements in muscle strength [56]. Currently, IVIG is reserved for those patients with LEMS who are unresponsive to standard immunosuppressive therapy.

Stiff-person syndrome

The stiff-person syndrome is a rare disorder characterized by severe episodic muscle rigidity and spasms associated with high titres of antibodies to glutamic acid decarboxylase (GAD). Anti-GAD antibodies inactivate GAD, the rate-limiting enzyme for the synthesis of gamma amino butyric acid (GABA), a major inhibitory neurotransmitter. There is good evidence from the only RCT conducted that IVIG significantly reduces muscle stiffness in this disease [57]. Because drugs that enhance GABA only produce a modest improvement in symptoms, IVIG is likely to be considered the treatment of choice.

Multiple sclerosis

The beneficial effects of IVIG in reducing the frequency of relapses in relapsing-remitting MS is of a similar magnitude to that achieved with beta-interferon and glatiramer acetate [58]. A recent Cochrane review of IVIG in MS concluded that while there was some evidence to support its use to prevent relapses in relapsing-remitting disease, there remained a need for further studies to enable more robust conclusions to be drawn [59]. In contrast, IVIG is of no demonstrable benefit in secondary progressive MS [60].

Intravenous immunoglobulin in primary antibody deficiency

At the inception of immunoglobulin replacement for primary antibody deficiency (PAD) in the 1950s no studies comparing intramuscular immunoglobulin (IMIG) with either placebo or a no treatment arm were contemplated or undertaken because immunoglobulin replacement made intuitive good sense in patients with endogenous B cell failure. Indeed, when the UK Medical Research Council trial of the efficacy of immunoglobulin replacement therapy in hypogammaglobulinaemia was set up in 1955 it was felt that a placebo arm would be unethical because of strong presumptive evidence from the United States that Ig replacement was effective in decreasing the frequency of infections in hypogammaglobulinaemia.

The first major randomized trials of immunoglobulin replacement therapy were therefore conducted with the advent of intravenous immunoglobulin (IVIG) in the 1970s and showed that IVIG was as good [61] or superior [62,63] to IMIG in reducing infection frequency in PAD even with the use of relatively small doses of IVIG at 0·15 g/kg. The question of the optimal dose of IVIG was addressed by Roifman *et al.* [64], who showed that maintenance of a trough serum IgG level in excess of 5 g/l using doses of 0·6 g/kg resulted in a greater reduction in infections and improvement in spirometric indices compared to those patients who received 0·2 g/kg. Subsequent studies designed [65–67] to answer the question whether more immunoglobulin is necessarily better have produced mixed results which are likely to be due to differences in study design, dose and the lack of a washout period between different dosage arms of the study. There is widespread acceptance however, amongst clinical immunologists that trough IgG levels should be maintained within the age matched normal reference range for patients with PAD with individual patients benefiting from higher trough levels. Several studies [68–70] document a decrease in the incidence of pneumonia in PAD once IVIG is commenced although the finding of asymptomatic progression of bronchiectasis [71] in some patients with common variable immunodeficiency (CVI) despite achieving trough IgG levels in excess of 5 g/l is worrying and suggests that factors other than infection may be driving lung damage in CVI.

IVIG as prophylaxis against sepsis in low-birth weight or preterm infants

Given that maternal transfer of IgG to the fetus occurs mainly after 32 weeks of gestation there has been much interest in the role of IVIG as prophylaxis against infection in preterm babies. Although early studies suggested some benefit, a Cochrane meta-analysis of 19 studies [72] including approximately 5000 preterm babies has shown that IVIG makes a marginal reduction to the frequency of sepsis but importantly does not reduce associated morbidity or overall mortality. The meta-analysis concluded that there is no justification for further randomized trials of IVIG in preterm or low birth weight infants.

Equally, the role of IVIG as adjunctive therapy for suspected or proven neonatal sepsis is not supported by a recent Cochrane meta-analysis [73] which showed that the reduction of mortality with IVIG was only of marginal significance.

Dermatological

The conditions with the greatest amount of published evidence are Kawasaki disease, therapy resistant dermatomyositis (see neurology section), toxic epidermal necrolysis and the blistering diseases (pemphigus vulgaris, bullous pemphigoid, epidermolysis bullosa acquisita, mucous membrane pemphigoid, linear IgA disease and gestational pemphigoid) in particular pemphigus vulgaris. Other conditions where the evidence consists mainly of case series or reports are atopic dermatitis [74], chronic immune urticaria [75–77], scleromyxoedema [78–82], pyoderma gangrenosum [83–88], pretibial myxoedema [89,90], erythema multiforme and psoriasis [91].

Kawasaki disease

Kawasaki disease is an acute febrile childhood vasculitic illness, first described in Japan in the 1960s by Dr Tomasko Kawasaki [92–94]. Following the decline of rheumatic heart disease, Kawasaki disease is the most common cause of acquired coronary artery disease in the developed world. The symptoms include prolonged fever, bilateral nonpurulent conjunctivitis, a polymorphus erythematous rash, changes in the oral mucosa and oedema and redness of the extremities with associated desquamation of the hands and feet. At the same time it emerged that many patients developed coronary artery abnormalities such as aneurysms, detectable on echocardiography. This was associated with a significant mortality rate from acute myocardial infarction.

There have been almost 300 publications including controlled trials and a Cochrane review on the use of IVIG in this disease [95–97]. The conclusions are that children fulfilling the diagnostic criteria for Kawasaki disease should be given as first line treatment a single dose of 2 g/kg of IVIG within 10 days of the onset of symptoms.

Toxic epidermal necrolysis

Toxic epidermal necrolysis (Lyell's syndrome) is a rare adverse cutaneous drug reaction characterized by an average mortality of 30%. No specific treatment exists to date. A proposed mechanism for TEN is extensive Fas-mediated keratinocyte apoptosis, a process that can be inhibited *in vitro* by anti-Fas antibodies present in IVIG [9]. The Stevens–Johnson syndrome (SJS) is considered to be a limited form of TEN characterized by mucous membrane lesions and skin blisters affecting < 10% of the total body surface area.

The therapeutic potential of IVIG in SJS and TEN has not been assessed in controlled randomized studies and more information is needed; however, a number of studies have shown a reduction in blistering and mortality with IVIG [98,99]. In a prospective open monocentre trial assessing IVIG at an average total dose of 2 g/kg in 34 consecutive patients 8·2 (24%) deaths were predicted and 11 were observed (32%) [100]; however, an unusually high mortality rate due to renal failure (six patients) was reported in this study. Taken together, the evidence suggests a potential benefit from a single cycle of 2 g/kg of IVIG with the possibility of some further improvement at higher doses (3 g/kg) on subgroup analysis. Many centres now use IVIG as first line treatment for TEN in the light of the available evidence.

Pemphigus vulgaris

Pemphigus vulgaris (PV) is an autoimmune blistering disease with autoantibodies to desmoglein 3 [101]. The disease can affect the skin and mucous membranes of the oral cavity, nose, eye, pharynx, larynx, oesophagus, anal canal, penis and vagina [102]. There are now more than 60 patients who have been treated with IVIG in the literature [103,104], the vast majority of whom responded to treatment with 2 g/kg given at monthly cycles. Once disease remission is attained it is possible in many cases to reduce and finally discontinue IVIG. In view of these encouraging results, a controlled trial of IVIG in therapy-resistant PV is needed to clarify its potential therapeutic role. This also applies to cicatricial pemphigoid [105].

Nephrology, rhematology and other uses

Systemic vasculitis

High-dose IVIG has been shown in open [106] and randomized studies [107] to be a useful adjunctive therapy in antineutrophil cytoplasmic antibody (ANCA)-positive systemic vasculitis (AASV) refractory to standard immunosuppressive therapy. The use of IVIG as sole therapy in AASV [108] without vital organ involvement has produced encouraging results in open trials but has not been extended to patients with major organ damage.

Although IVIG has been used in single-cases or small-cases series of patients with other small vessel vasculitides with apparent benefit, its use in mixed cryoglobulinaemic vasculitis is fraught with danger due to the risk of acute renal failure caused by the deposition of immune complexes composed of exogenous IgG and the IgM rheumatoid factor component of mixed cryoglobulins [109].

Systemic lupus erythematosus (SLE)

The reported success of high dose IVIG in open-cases series of patients with SLE [110] is yet to be subjected to the critical rigour of a randomized placebo-controlled trial. In patients with proliferative lupus nephritis who have entered remission following standard immunosuppressive therapy, monthly IVIG was shown to be as efficacious as regular cyclophosphamide in maintaining remission [111]. Whether IVIG will gain wider acceptance as a therapeutic agent in SLE is debatable, given the recent success of Rituximab in severe lupus [112].

IVIG in streptococcal toxic shock syndrome

The success of adjunctive IVIG therapy in an open series of patients [113] with streptococcal toxic shock syndrome (STSS) is supported by the finding that IVIG contains superantigen-neutralizing antibodies and the ability of post-IVIG plasma from patients with STSS to completely block streptococcal toxin-induced cytokine production [114]. Given its rarity, there are no randomized trials of IVIG in STSS.

Birdshot retinochoroidopathy and autoimmune uveitis

Birdshot retinochoroidopathy (BRC) is a bilateral autoimmune posterior uveitis which, in its progressive form, frequently requires immunosuppressive therapy. The results of open studies in both BRC and uveitis are encouraging; however, there have been no randomized controlled trials to support these initial findings [115,116].

Are all IVIG preparations equally efficacious?

While all currently available IVIG preparations are licensed for use in antibody deficiency, not all products have received a license for the wide range of immunomodulatory indications for which IVIG is used. Because differences in the manufacturing process affect opsonic activity [117], Fc receptor function [118] and complement fixation [119] it is best not to consider all IVIG preparations as a generic product. Studies comparing the efficacy of different IVIG products have only been performed in Kawasaki disease [120]. More recently, adverse reactions were noted in a group of patients with primary antibody deficiency whose usual IVIG preparation was replaced by a new product [121]. For the above reasons and the potential difficulty in tracking any future outbreak of IVIG-associated viral transmission, it would be prudent if patients requiring indefinite treatment are maintained on the same IVIG product, irrespective of whether IVIG is used for antibody replacement or immunomodulation.

Table 2 summarizes the important properties of IVIG preparations currently available in the UK. Patients with high titres of anti-IgA antibodies on a background of total IgA deficiency should ideally be treated with a preparation containing low levels of IgA to avoid the rare occurrence of anaphylaxis. For patients with pre-existing renal disease, sucrose containing products are best avoided since the risk of renal impairment is greatest with those IVIG preparations containing sucrose as a stabilizer. A classification and summary of the more important and frequently encountered IVIG-induced adverse effects is shown in Table 3, however, a more detailed account is beyond the scope of this article and the reader is referred to the review by Pierce *et al.* [122].

Summary

There has been a rapid expansion in the use of intravenous immunoglobulin (IVIG) for an ever growing number of conditions. It is a product with an excellent safety record without the side effects of steroids or other immunosuppressive agents. There have been numerous recent advances in our understanding of the mechanisms of action of IVIG in many of the conditions for which it is being used, but there is still much to be learned. IVIG has had a major impact in neurology, haematology, immunology, rheumatology and dermatology. The limitations for IVIG are cost of the

Table 2. Adverse effects of intravenous immunoglobulin therapy.

Immediate infusion-related†	Transmission of infective agents†	Consequences of increasing serum IgG††
Mild to moderate reactions – headaches, backache, chills, nausea, muscle pain – occur in approximately 1% of infusions and are largely rate-related	Hepatitis C – several outbreaks to date; additional anti-viral step introduced by most manufacturers following last outbreak in 1994	Renal – reversible renal impairment (majority of cases), acute renal failure in mixed cryoglobulinaemia
Severe – anaphylaxis may occur very rarely in IVIG recipients who have high titres of anti-IgA antibodies	?Prions – potential risk;no documented cases to date	Haematological – cerebral and coronary thromboses, acute haemolysis, neutropenia Neurological – acute aseptic meningitis Dermatological – eczema, urticaria, erythema multiforme cutaneous vasculitis

†May occur with either low or high-dose IVIG; ††predominantly associated with high-dose IVIG.

Table 3. Properties of IVIG preparations currently available in the UK.

Product	Formulation	Manufacturing procedure	Additional antiviral step	IgA content mg/l	Carbohydrate stabilizer
Flebogamma	Liquid	PEG Precipitation DEA sephadex	Yes	4.3	D-Sorbitol
Gammagard-SD	Powder	DEA sephadex	Yes	0.4–1.9	Glucose Glycine
Octagam	Liquid	pH4	Yes	<100	Maltose
Scottish National BTS	Powder	pH4	No	920	Sucrose
Sandoglobulin	Powder	pH4	No	720	Sucrose
Sandoglobulin NF	Liquid	pH4	Nanofiltration	<15	None
Vigam-S	Liquid	Ion-exchange chromatography	Yes	5	Sucrose

Note that while the manufacturing process for all IVIG products have proven in-built antiviral procedures, some manufacturers have introduced an additional step.

preparation itself and the logistical problems associated with its administration. Many of the side effects are managed easily by careful screening of the patient prior to treatment, premedication with analgesics and antihistamines and adjustment of infusion rate. It is likely, however, that side effects will be more frequent as the dose given increases and effects on plasma viscosity become greater [122]. It will be important to increase the evidence base for IVIG in many conditions to define its therapeutic role. In addition, there have been very few dose-ranging studies for hdIVIG and fewer still of which adjunctive agents (including biological agents such as rituximab and daclizumab) might offer the best therapeutic combinations.

Although not established, the use of IVIG is being studied in a range of conditions including heart failure, mycobacterial infection, adult respiratory distress syndrome, transplantation, fibrosis, connective tissue disease, encephalitis, epilepsy and even Alzheimer's disease. Should IVIG prove to be of efficacy in these settings it is likely to have major implications for drug budgets as many of the conditions are very common and place great strain on the world's supply of IVIG itself. Future studies will therefore need to address questions of efficacy, pharmacoeconomics, dose, adjunctive therapies and mechanism of action which may point the way to novel treatment strategies beyond IVIG. It is also clear, however, that controlled trials in many of the rare conditions may be very difficult to carry out and approaches such as prospective disease registries may be needed.

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